#22
1-18-01
Done

RECEIVED
JAN 12 2001
TECH CENTER 1600/2900

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Howard L. Elford

Serial No. 09/123,620

Filed: 7/28/98 Group Art Unit 1614

THERAPEUTIC PROCESS FOR INHIBITING NF-kB Examiner K. Fonda

Docket No. HEBVR-5

OIPE JAN 08 2001 PATENT & TRADEMARK OFFICE 3C1115

Commissioner of Patents and Trademarks

Washington DC 20231

BRIEF ON APPEAL

1. The above-entitled application will be assigned to Molecules For Health, Inc. 3313 Gloucester Road, Richmond VA 23277. The inventor in the matter of the above-entitled application is the principal stockholder of that small entity corporation.

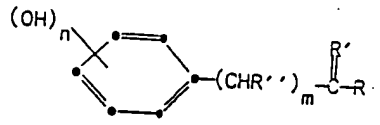
2. There are no related appeals or interferences.

3 **STATUS OF CLAIMS**

Claims 2-11 and 14 have been finally rejected and are under appeal;

4. **SUMMARY OF THE INVENTION**

This invention provides a therapeutic process for the inhibition of NF-kB in whose cells NF-kB has been activated , which process comprises administering to a mammal in whose cells NF-kB has been activated and who is in need of treatment, an NF-kB inhibitory amount of a free-radical inhibiting amount of a compound of the structure



wherein n is 2-5, m is 0 or 1,R is NH , NHOH, OC_{1-3}alkyl or O-phenyl, R' is O, NH or NOH, R" is H or OH, acylated phenol derivatives of said drugs and pharmaceuticall-acceptable acid-addition thereof. There are also claims to an identical

process wherein the NF-kB inhibitor is a free-radical scavenger or is a ribonucleotide reductase inhibitor.

5. **CONCISE STATEMENT OF THE ISSUES FOR REVIEW**

All claims are rejected as obvious in view of Van't Riet et al U.S.Patent4,623,659.

REJECTION OF THE CLAIMS UNDER 35 U.S.C. 103 (a)

Claims 2-11 and 14 are rejected as obvious under 35 U.S.C. 103(a) over VAN't Riet et al on the ground that the compounds disclosed therein are known to be Ribonucleotide Reductase Inhibitors (RRI's) and free-radical scavengers. It is the Examiner's opinion that any RRI must of necessity be an anti-oxidant and that anti-oxidants are known to inhibit NF-kB. However, The Examiner goes on to say, without citing any reference, that one of ordinary skill in the art would recognize that RRIs and free radical scavengers are also all anti-oxidants. This statement is incorrect. It should be noted that enzymes like ribonucleotide reductase can be destroyed or their action inhibited by means other than oxidation. For example, what if ribonucleotide reductase acts by initiating a free-radical reaction and the Van't Riet et al compounds are free-radical-scavengers. Or perhaps it acts by combining with the surface of the reductase at sites which are necessary for reaction with a ribonucletide?

It should also be emphazisd that oxidation-reduction reactions and free-radical chain reactions involve complely disparate chemistry and are never suggestive of one another. Oxidation invariably involes a change in valence for the compound being oxidized. For example, in an anti-oxidant mercaptan, the SH group would be oxidised first to a sulfoxide and then to a sulfone. On the other hand, a free-radical scavenger would simply react with a free-radical to pick up the odd electron and eventually combine with another free-radical incapable of

continuing the free-radical chain reaction to form a new compound. No chain reactions are involved in oxidation reactions. The oxidizing agent and the substrate react to change the valence state of each and neither is involved in any continuing reaction.

Before stating Appellant' position in this matter, Appellant would like to summarize certain aspects of free-radical chemistry which are involved in the claimed processes. There are two ways of blocking a free-radical reation. First, destroy rhe compound which initiates the free-radical reaction chain-here, a hydroperoxide. Alternatively, a free-radical inhibitor can be added to the reaction mixture to end the free-radical chain initiated by decomposition of the hydroperoxide. For example, in making BUNA-S, a free radical reaction is started by addition of a peroxide, which decomposes with heat to yield free-radicals, to the mixture of styrene and butadiene. When the reaction has progressed sufficiently far to give a rubber of the desired characteristics, a free-radical scavenger is added to stop th epolymerization from proceding further. In the instant case, the Examiner's anti-oxidant compounds would destroy the peroxide initiator, whereas Appellant's free-radical scavengers all attack and prevent the chain reaction from starting. These are completely different types of chemistry.

In order to bolster his rejection, the Examiner has cited a paragraph from page 42 of Casarett & Doull's Toxcology, Fifth Edition which reads as follows: "Peroxidase free-radicals are eliminated by electron transfer to glutathione, which is reversed by NAPDH-dependant glutathione reductase. Thus, glutathione plays an important part in the detoxification of both electrophiles and free-radicals". The Examiner then states that "a compound which is the inhibitor of a reductase, or a free-radical scavenger, must necessarily be an oxidizing agent".

This statement is incorrect. In a free-radical chain reaction, the free-radical has an extra electron which it transfers to a substrate and thus accomplishs a one-electron oxidation of the substrate. This new free-radical becomes a one electron oxidizing agent in its own right, reacts with a second substrate molecule to yield the product plus another free-radical, and so on till the chain reaction terminates. It is thus apparent that the substrate is a one-electron reducing agent. It is, however, Appellant's position that to use the term "anti-oxidant" when referring to free-radicl chain reactions and one-electron transfers is to torture the accepted meaning of "anti-oxidant" beyond recognition. Anti-oxidants prevent the reaction of oxygen, peroxides etc with substrates. These reactions all involve two-electron transfers which <u>permanently</u>, and not transitorially, change the oxidation state of the compound being oxidized. In fact, the real basis of the rejection seems to be that it would be "obvious to try" the van't Riet compounds. This type of rejection is no longer tenable

Appellant submits that the rejection of the claims under 35 USC 103(a) has been overcome by the above arguments and should be withdrawn.

As can be seen from the above arguments, Appellant's claimed free-radical scavengers do not actually "oxidize" anything. They have the ability to terminate a free-radical chain reaction, and nothing more. Thus, by citing van't Riet et al, Appellant has admitted nothing of relevance to the claimed procedures.

Appellant submits that the rejection of the claims under 35 U.S.C. 103(a) has been overcome by the above arguments and should be withdrawn.

CONCLUSION

Appellant has demonstrated by argument, that the rejection of the claims under 35 U.S.C. 103(a) was based upon an expansion of the customary meaning of the term "anti-oxidant" so that the cited prior art could be said to render obvious Appellant"s claims. This farfetched application of the term "antioxidant" was made with the use of hindsight based upon Appellant's own disclosures and not by anything taught by the cited prior art. Allowance of the claims is repectfully requested.

Respectfully submitted,

James L. Rowe Reg. No. 18448

Attorney for Appellant

2726A Marquette Manor Drive

Date: 1-4-01 Indianapolis IN 46268

Date:

ADDENDUM

CLAIMS ON APPEAL

2) A process according to Claim 14 in which the external agency activating NF-kB in an inflammatory process includes, but is not limited to, a cytokine, an activator of protein kinase B, a virus or an oxidant.

3) A process according to Claim 14 in which the external agency activating NF-kB is a drug or radiation administered to the host mammal in a chemotherapeutic process used in the treatment of cancer.

4) A process according to Claim 14 in which the administered NF-kB inhibitor is a free-radical scavenger.

5) A therapeutic process according to Claim 14 in which the NF-kB inhibitor is N,3,4-trihydroxybenzamide.

6) A therapeutic process according to Claim 14 in which the NF-kB inhibitor is N,3,4,5-terahydroxybenzamide.

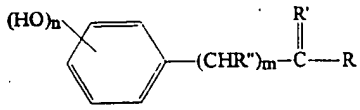
7) A therapeutic process according to Claim 14 in which the NF-kB inhibitor is N, 3,4-tetrahydroxybenzimideamide.8) A therapeutic process according to Claim 14 in which the NF-kB inhibitor is a ribonucleotide reductase inhibitor.

9) A process according to Claim 14 in which the external agency activating NF-kB is the reslt of a tissue transplant, an organ transplant or a cell transplant in a mammal.

10) A process according to Claim 14 in which the external agency activating NF-kB is arteriosclerosis.

11) A process according to Claim 14 in which the external agency activating NF-kB is diabetes.

14. A process for inhibiting NF-$_{\kappa}$B in a mammalian cell in which NF-$_{\kappa}$B has been activated by an agency external to said cell which comprises administering to the mammal in whose cells NF-$_{\kappa}$B has been activated an NF-$_{\kappa}$B inhibiting amount of a drug represented by the formula:



wherein n is 2-5, m is 0 or 1, R is NH_2, NHOH, OC_{1-3}alkyl, or O-phenyl, R' is O, NH or NOH, R" is H or OH, or a pharmaceutically- acceptable acid addition salt or acylated phenol derivative thereof.